Prostheses with biologically active coatings

The subject of the invention is the use of biologically active compounds for the coating of prostheses. It relates in particular to the coating of stents comprising a biologically active coating.

It is known that the treatment of stenoses of the coronary arteries was revolutionized by coronary angioplasty, which consists of opening the stenosis with a balloon. This technique was improved by using a metal arterial endoprosthesis, called a "stent", in order to prevent retractile cicatrization of the artery causing restenosis, i.e. the reappearance of the stenosis. However, in a good number of cases, varying from 20 to 35% depending on the type of lesion, it was found that the insertion of a stent in an artery causes a restenosis linked with a neointimal hyperplasia, which results both from an excess of scar tissue and from a reaction to the foreign body. In order to overcome these problems, it was proposed to coat the stents with medicated substances capable of combating restenoses.

Of the strategies proposed, that which consists of using molecules with anti-proliferative effect aroused much interest. During the first 6 months of insertion of stents with a coating of anti-proliferative compounds, no restenosis was indeed observed.

However, these molecules have the drawback of also inhibiting the scarring phase, which produces a risk of late thrombosis on a bare metal body, as well as the creation of a space between the stent and the artery wall by dilatation of this wall (hereafter called positive remodelling).

On animal models, a late restenosis phenomenon was also observed.

It therefore appears that, although the use of stents as pharmacological platforms allowing delivery of a medicament constitutes a beneficial approach, the therapeutic families proposed up until now are not satisfactory.

The inventors found that, by following another medication-based approach, based on the inhibition of the extracellular matrix, it was possible to inhibit up to 95 % of the scar tissue

responsible for hyperplasia and preventing intra-stent restenosis. This result proved to be applicable generally to the coating of other prostheses.

The aim of the invention is therefore to use novel compounds in the development of coatings for prostheses.

It also relates, as new products, to these platforms and prostheses, in particular stents having such coatings.

The use according to the invention is characterized by the use of inhibitors of the cellular matrix to develop a pharmacologically active coating on a prosthesis.

Surprisingly, such coatings make it possible, in a situation of mechanical trauma of the tissues causing an inflammatory response, to avert arterial restenosis.

Unlike the prior art strategies mentioned above, such regulators do not affect the cell cycle and therefore do not have a deleterious effect on the endothelium which may result in the appearance of late thromboses, a positive remodelling or a late restenosis.

The inhibition of the synsthesis of the extracellular matrix makes it possible to keep a healthy wall and not adversely affected by the loss of or damage to cells, which also allows thrombosis phenomena to be averted.

Preferably, the inhibitor of the extracellular matrix is a natural inhibitor of TGF β-1.

Among appropriate compounds, will be mentioned proteoglycanes, such as decorin and/or a decorin peptidic fragment, hyaluronic acid, or still anti-TGF β-1antibodies.

In a preferred embodiment of the invention, this is more particularly decorin or a decorin peptidic fragment. The release of these compounds from a coating of prosthesis, particularly a stent, makes it possible to inhibit with a high efficiency matrix extracellular secretion and to prevent main risks of positive remodelling and late arterial restenosis.

The use of decorin and/or a decorin fragment also advantageously enables to prevent the deposit of fibrine or the atrophy of the stent under lying walls, such as observed with previously used drugs.

According to another aspect, the invention also aims to provide as new products prostheses characterized in that they comprise a coating containing a therapeutically effective amount of a TGF β-1 inhitor.

By "therapeutically effective amount" is meant an amount which allows the inhibition of the surplus of extracellular matrix produced in response to the trauma of the inserted prosthesis.

Preferred prostheses more particularly comprise a therapeutically effective amount of decorin and/or a peptidic decorine fragment.

The prostheses which are more specifically concerned correspond to implantable devices or endoluminal prostheses, in particular endovascular, urological, respiratory or digestive prostheses.

The antifibrotic effect of decorin is advantageously also exploited with prostheses outside arterial application, in particular in urological, digestive, bronchopulmonary applications.

Other characteristics and advantages of the invention are given in the following examples.

Production of a stent with a bioactive coating of decorin and arterial application

Operating according to standard techniques, a biodegradable coating based on polymers, containing a pharmacologically active quantity of decorin, allowing the release of active ingredient over 30 days, is applied to a metal stent.

The stent is placed into the coronary artery in a patient. After 3 months of observations, no restenosis phenomenon was observed.

CLAIMS

1. Use of inhibitors of the extracellular matrix, in order to develop a pharmacologically active coating on a prosthesis.

2. Use according to claim 1, wherein the inhibitor of the extracellular matrix is a natural inhibitor of TGF β-1.

3. The use according to claim 2, wherein the TGF β-1 inhibitor is selected in the group comprising proteoglycanes, such as decorin and/or a decorin peptidic fragment, hyaluronic acid, or still anti-TGF β-1antibodies.

4. The use according to claim 2, wherein the inhibitor is decorin and/or a peptidic fragment of decorin.

5. Prostheses, characterized in that they comprise a coating containing a therapeutically effective amount of a TGF β-1 inhibitor.

6. The prostheses according to claim 1, characterized in that they comprise a therapeutically effective amount of decorin and/or of a peptidic fragment of decorin.

7. The prostheses of claim 5 or 6, characterized in that they are implantable devices or endoluminal prostheses, in particularendóvascular, urological, respiratory or digestive prostheses.